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Immunovirological and Biochemical Changes in Nigerian Patients with Hepatitis B Coinfection on Antiretroviral Therapy

Jesse Abiodun Otegbayo[1], Titilola Stella Akingbola[2], Joshua Odunayo Akinyemi[3], Kayode Solomon Adedapo[4], Georgina Njideka Odaibo[5], Yetunde Adebisi Aken Óva[2], David Olufemi Olaleye[5], Isaac Folorunsho Adewole[7], Robert Murphy[8], Phylis Kanki[9]

[1]Departments of Medicine, University of Ibadan, Ibadan, Nigeria; [2]Department of Haematology, University of Ibadan, Ibadan, Nigeria; [3]Department of Epidemiology and Biostatistics, University of Ibadan, Ibadan, Nigeria; [4]Department of Chemical Pathology, University of Ibadan, Ibadan, Nigeria; [5]Department of Virology, University of Ibadan, Ibadan, Nigeria; [6]Department of Haematology, University of Ibadan, Ibadan, Nigeria; [7]Department of Obstetrics and Gynaecology, University of Ibadan, Ibadan, Nigeria; [8]Department of Infectious Diseases, North-western University Feinberg School of Medicine, Chicago, USA; [9]Department of cancer Biology, Harvard School of Public Health, Harvard University, Boston, USA.
Email: otegbayoa@comui.edu.ng

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ABSTRACT

Hepatitis B virus (*HBV*) *co-infection with HIV is high among Nigerians. Some studies have suggested impaired CD*4 *recovery among coinfected patients compared to the HIV mono infected. This retrospective study of treatment-naïve HIV infected patients was aimed at determining the trend of changes in CD*4$^+$ *counts*, *HIV-RNA*, *renal and liver function tests in response to combined antiretroviral therapy* (*CART*). *A questionnaire was utilised to extract clinical and laboratory data of HBV co infected HIV/AIDS patients before treatment and at six*, *twelve and eighteen months of therapy with CART. Findings were compared to those of HIV mono infected. Relevant statistical instruments were used to analyse for comparisons of means of Log*$_{10}$ *HIV viral load and CD*4 *count using SPSS package* 15.0. *All levels of significance were at* 5%. *Two thousand five hundred and sixty two patients were analysed. Of these*, 354 (13.8%) *were HBsAg positive. Majority* (63.1%) *were females. Most of the recruited patients were on combivir and nevirapine. The median CD*4 *count for the HBsAg negative was 104 cells*/(*mm*^{3} *IQR* 34-171) *and it was significantly higher than those of the positive* (91 *cells*/*mm*^{3}) ($p < 0.05$). *ALT and AST were higher among HBsAg positives*, *while urea and creatinine levels were similar. The median change in CD*4 *count from baseline and during the course of therapy were similar in the two groups. Similarly*, *virological responses were not different in the two groups at the various time points. In conclusion no significant difference in the rate of CD*4 *recovery and HIV-RNA decline in among coinfected and monoinfected HIV patients at different stages of therapy.*

Keywords*: *Hepatitis B*, *Coinfection*, *CD*4, *Viral Load*, *Antiretroviral*, *Nigeria

1. Introduction

Hepatitis B virus (HBV) is a common major endemic infection in Nigeria [1,2] and its association with common major liver diseases is well established in our environment [3,4] as in other parts of the world. HIV/AIDS continue to receive significant attention and a sizeable proportion of the health care budget because of the yet to be conquered pandemic. Previous studies in Nigeria have shown a significant hepatitis B and C virus co-infection with HIV infection [5,6]. These studies however showed that hepatitis C, either as mono-infection or as co-infection with HIV infection is relatively low compared with HBV. Many of the antiretroviral drugs in current use are associated with hepatotoxicity among other side-effects. Hepatotoxicity of antiretroviral drugs especially co-infected patients with hepatitis viruses is a major concern, with increasing incidence of liver lidease [7]. Some studies have addressed the immunological (CD4$^+$) and viral (HIV-RNA) responses in HIV/AIDS patients on combined antiretroviral therapy (CART). Micheloud *et al.* in their study among HCV-coinfected paediatric patients

found no difference in clinical, immunological and viral response to CART over a six year period, save for increased transaminases among HCV coinfected [8]. A meta-analysis had shown that patients with HIV-HCV coinfection have less immune reconstitution, as determined by CD4 cell count after 48 weeks of CART, than patients with HIV monoinfection [9] suggesting some influence of hepatitis C on immunologic recovery in HIV infection. Clinical progression of HIV-1 disease after starting potent antiretroviral therapy is accelerated by concomitant infection with HCV. De Luca *et al.* concluded in their study that compared with patients without HCV coinfection, coinfected patients showed impaired $CD4^+$ cell recovery, despite similar virologic response to HIV-1 therapy [10]. Since HBV is the most important co-infection among Nigerians, we embarked on a retrospective study of CART-naive HIV infected patients. The objective of the study was to determine the trend of changes in $CD4^+$ counts, HIV-RNA load as well as biochemical, renal and liver function tests in response to CART.

2. Materials and Methods

The database of the PEPFAR clinic at the University College Hospital, Ibadan, Nigeria was searched between January 2006 and December 2007 to retrieve the presented data. The total number of patients on CART on the PEPFAR database at the time of data extraction was 4354 as at December 2007. A questionnaire was designed to extract the clinical data, liver function tests, $CD4^+$ counts and HIV viral load as well as the antiretroviral combination of patients who were HBV-coinfected and compare with those who were mono infected with HIV. Hepatitis B surface antigen was detected from sera using commercially available 3rd generation ELISA technique (ABBOT Murex, Germany), while HIV antibody was initially detected by ELISA test followed by confirmation test using the Western blot hybridization. HIV-RNA quantification was by reverse transcriptase polymerase chain reaction (RT-PCR), with a lower detection rate of 400 copies/ml. All patients with HIV were tested for HBsAg at first visit, but HBeAg, anti-HBeAg and HBV-DNA were not determined. The results were noted at entry (baseline) before commencement of CART. HIV-RNA, $CD4^+$ counts, ALT, AST, urea and creatinine were then determined at six, twelve and eighteen months respectively. Only patients with HIV-1 and HIV-2 with detectable HIV-RNA and $CD4^+$ count of $\leq$ 250 cells/ul were included in the study. Patients who were anti-HCV positive were excluded. Also excluded were those that had missing CD4, ALT and AST or were non-compliant with medication and those who were not able to do CD4 count at the time of entry due to equipment breakdown.

2.1. Statistical Methods

Quantitative variables were assessed for normality using visual inspection of box-plots and normal probability plots. The Chi square test was used to assess differences in frequencies for categorical variables. Levene's statistic was used to assess equality of variance between groups before independent two-sample tests for comparisons of means of Log_{10} HIV viral load at baseline. Given the significant non-normality of CD4 count and liver function test results, a non-parametric two-sample (Mann-Whitney) test was performed to determine differences in their distribution between HBsAg status. Six hundred and sixteen cases with missen values (for follow up CD4 count/Viral load, AST/ALT) were excluded list wise automatically by the statistical software. The generalized linear model repeated measures analysis was performed to assess the effect of HBsAg status on treatment over time. Sex, education, baseline AST and ALT were adjusted for, and all statistical tests were carried out at the 5% significance level using SPSS 15.0. Ethical approval was obtained from the Joint University College Hospital, Ibadan/University of Ibadan Institutional Review Board.

3. Results

3.1. Socio-Demographic and Clinical Characteristics

Two thousand five hundred and sixty two patients who had sufficient retrievable data were included in the analysis. Of the 2562 patients, 354 (13.8%) were HBsAg positive. Majority (63.1%) were females. In terms of educational attainment, secondary (37.9%) and primary (29.7%) were the most common. A little above half (58.1%) were married. **Table 1** shows the socio-demographic and clinical characteristics of the patients according to the HBsAg status. The mean ages were (36 + 8.9) years and (37.1 + 9.9) years for the HBsAg positive and negative patients respectively ($p > 0.05$). There is a higher proportion of males (48.3%) in the HBsAg positive group than in the HBsAg negative (35.1%). ($p < 0.05$). HBsAg positivity was also found to be higher among those with primary (32.9%) and secondary (41.7%) level education ($p < 0.05$).

The median CD4 count for the HBsAg negative was 104 cells/mm^3 (IQR 34-171) and it was significantly higher than those of the positive (91 cells/mm^3) ($p < 0.05$). Similar pattern was observed for ALT and AST with the HBsAg negative recording significantly lower values. Urea and creatinine levels did not show any significant difference between the two groups of patients.

3.2. Immunological and Virological Response

The median change in CD4 count from baseline time was

similar in the two groups (**Figure 1**). At 6 months, the median change was 143 cells/mm^3 and 148 cells/mm^3 for the negative and positive respectively. Although the median change at 18 months was higher for the positives (218 cells/mm^3) than negatives (206 cells/mm^3), the difference did not attain statistical significance ($p > 0.05$). A generalized linear model was fitted for CD4 count change to adjust for some baseline characteristics that differs between the groups. Results from the model shows that neither of the covariates nor HBsAg status affects CD4 count recovery. HBV status, education, ALT and AST all did not affect CD4 count recovery (**Table 2**).

The virological response was similar in the two groups at the various time points (**Figure 2**). At 6 months, the

Table 1. Clinical and demographic characteristics of subjects.

Characteristic	HBV+ (n = 354)	HBV– (n = 2208)	p-value
Age in Yrs Mean(SD)	36.1 (8.9)	37.1 (9.9)	0.076
Sex			
Male	48.3	35.1	0.001
Female	51.7	64.9	
Education			
None	5.2	9.7	
Primary	32.9	29.2	0.011
Secondary	41.7	37.3	
Tertiary	20.1	23.8	
Marital status			
Divorced	4.6	4.3	
Married	59.8	57.9	0.415
Separated	12.3	10.9	
Single	13.7	13.5	
Widowed	9.7	13.4	
Baseline			
CD4 count, Median (IQR)	91.5 (32 - 152)	104 (34 - 171)	0.02
Log_{10} Viral Load, Mean (SD)	5.029 (0.85)	5.044 (0.91)	0.787
AST, Median (IQR)	49.0 (33.8 - 69.2)	40.0 (29.0 - 63.0)	0.005
ALT, Median (IQR)	31.0 (20 - 40)	27.0 (17 - 41)	0.004
Urea, Median (IQR)	19.0 (15.0 - 28.0)	19.0 (14.0 - 28.0)	0.731
Creatinine, Median (IQR)	0.8 (0.6 - 1.0)	0.8 (0.6 - 1.0)	0.281

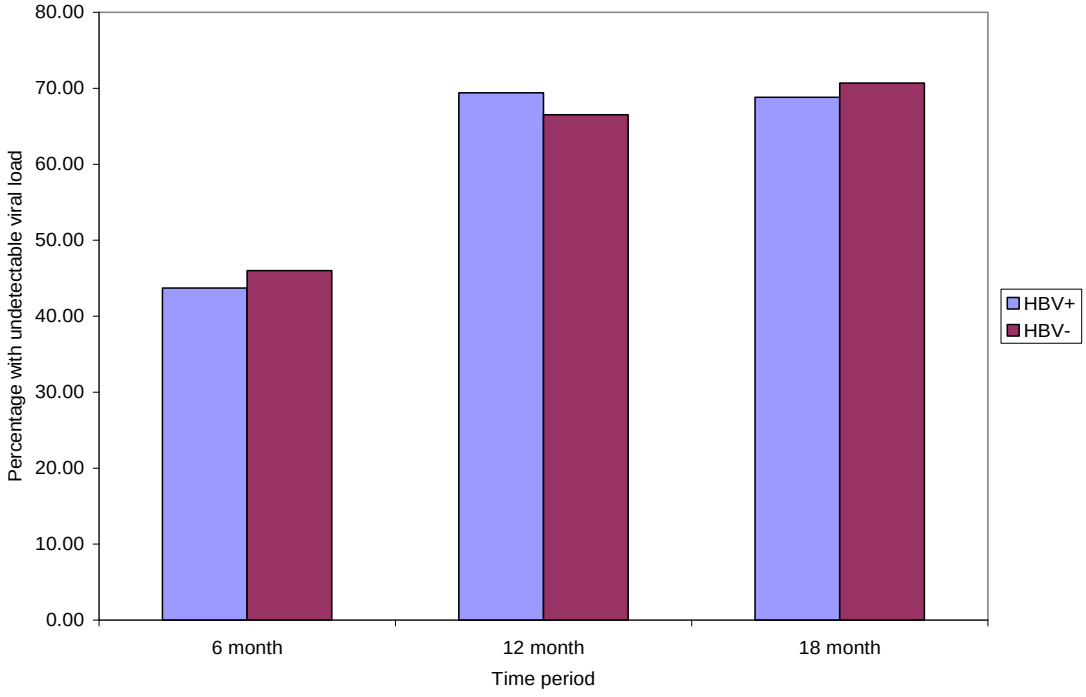

Figure 1. Proportion of patients by HBV infection status who achieved viral suppression.

percentage of patients who had achieved viral suppression (HIV RNA level < 500 copies/mL) was 46.7% in the negative group and 43.3% in the positive group ($p > 0.05$). The percentages at 18 months were 71.0% and 68.8% for the negatives and positives respectively. Repeated measures analysis showed that HBsAg status did not have any effect on viral suppression over time (**Table 2**).

3.3. AST, ALT, Urea and Creatinine

At baseline, ALT and AST levels were higher for the HBsAg positive patients ($p < 0.05$). The levels of these parameters at 6, 12 and 18 months are shown in **Table 3**. at the time points, these parameters were similar for the two groups of patients. Majority of the monoinfected

Table 2. Summary results for GLM repeated measures model for CD4 count and Log_{10} RNA Viral Load over time.

Variable	CD4 count		Log_{10} RNA Viral Load	
	Model coefficient (β)	95% Confidence Interval for β	Model coefficient (β)	95% Confidence Interval for β
Baseline ALT	0.16	–0.60 - 0.92	0.003	–0.001 - 0.007
Baseline AST	–0.06	–0.42 - 0.30	–0.001	–0.003 - 0.001
HBV	12.79	–33.08 - 58.65	0.063	–0.192 - 0.319
Gender	55.78	22.52 - 89.04*	–0.002	–0.187 - 0.183
Education	10.35	–6.69 - 27.39	–0.002	–0.137 - 0.054
Marital Status	–8.37	–25.52 - 4.7	–0.017	–0.09 - 0.056
Baseline CD4	0.87	0.69 - 1.00*	–0.001	–0.002 - 003
Baseline Log_{10} RNA Viral Load	25.85	3.94 - 47.75*	–0.014	–0.135 - 0.106
HAART regimen	40.49	–17.42 - 98.39	–0.019	–0.353 - 0.314

* $p < 0.05$; Model $R^2 = 0.216$

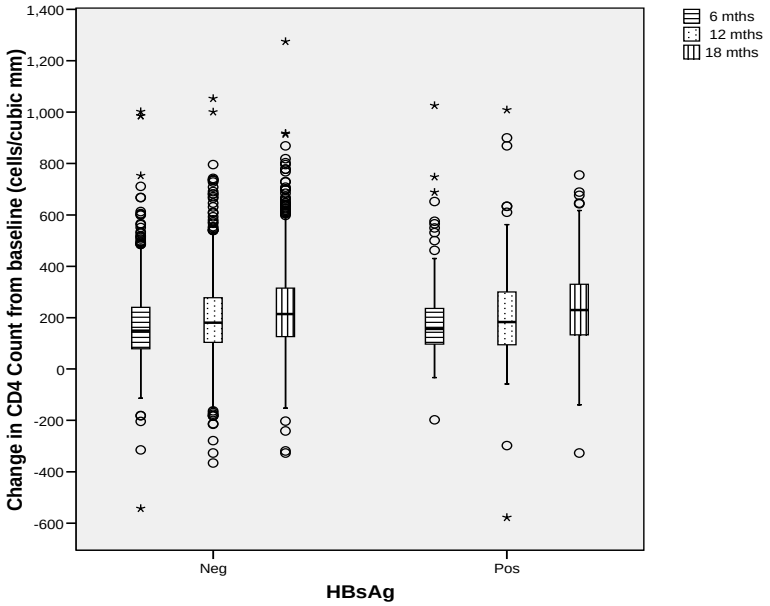

Figure 2. Change in CD4 counts from baseline.

Table 3. Laboratory parameters of subjects over time by HBV status.

Characteristic	6 month			12 month			18 month		
	HBV+	HBV–	p-value	HBV+	HBV–	p-value	HBV+	HBV–	p-value
ALT	30.0 (19 - 42)	27.0 (20 - 41)	0.689	26.0 (16.0 - 36.8)	23.0 (15.8 - 39.3)	0.692	16.0 (15.0 - 31.8)	23.5 (16.0 - 30.8)	0.860
AST	41.0 (30 - 68)	35.0 (26 - 49)	0.131	NA	NA		NA	NA	
Urea	21.0 (14 - 26)	18.0 (14 - 24)	0.338	18.5 (13.5 -26.5)	20 (13.0 - 24.5)	0.335	20.0 (18.0 - 31.0)	21.5 (13.3 - 30.0)	0.865
Creatinine	1.0 (0.8 - 1.1)	0.9 (0.7 - 1.0)	0.426	0.85 (0.7 - 1.0)	0.9 (0.7 - 1.0)	0.075	0.6 (0.5 - 1.0)	0.7 (0.5 - 1.1)	0.224

Median (IQR).

patients were on combivir and nevirapine, while the coinfected patients were mainly on truvada and nevirapine.

4. Discussion

This study has further shown a high HBV coinfection rate among our patient cohorts as previously noted by us and other authors in Africa [6,11,12] but higher than values obtained in the Western world with lower incidence of HBV [13,14]. The preponderance of the female gender had been suggested to be due to the fact that women may be more sensitive to changes in their health and probably socioculturally conditioned to seek health care more than men [6]. The significantly higher coinfection among men compared with women in spite of a predominant female gender affected with HIV is likely a reflection of HBV prevalence among the general population which has been noted to be higher amongst men [15]. The lower prevalence of coinfection among the better educated individuals generally could be due to the level of awareness that may be associated with education and therefore behaviours and practices that may reduce HBV transmission [16]. It is however surprising that no difference in HBV prevalence was found across the different marital status. It would have been expected, arguably though, that divorcees and the unmarried would be more exposed to transmission of HBV sexually. This phenomenon might be confirming the well known fact that HBV transmission is mainly horizontal in childhood among Africans. Ola *et al.* however found out that HIV monoinfection is commoner among married people (70.4%), suggesting heterosexual transmission of HIV in our environment as previously documented [16]. It would appear that the immunological status of HBV coinfection and monoinfection is similar, as evidenced by the similar CD4 counts in HIV monoinfected and HIV-coinfected at the start of CART. Similar observations were made Idoko *et al.* in the Northern part of Nigeria [17]. It is evident from our study that CART has no influence on CD4 recovery regardless of HBV status with time and duration of therapy. Idoko *et al.* however found an association with Hepatitis B e antigen (HBeAg) and CD4 T-cell recovery and HIV-RNA clearance [17]. Apart from the higher baseline values of transaminases among HBV coinfected patients, no temporal difference was observed in the normalization of ALT, urea and creatinine among coinfected and monoinfected patients, suggesting that HBV status did not significantly influence the immunovirological response to CART, renal function and transaminase levels. The retrospective nature of this study and our inability to determine the date of acquisition of both HIV and HBV (acute or chronic), as well as unavailability of HBV DNA are some of the limitations of our study. The exclusion of subjects with missen data may also affect the result as it is unclear whether such cases were missing for reasons connected with the study outcome.

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